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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/754,115	01/07/2004	Timothy D. Hey	DAS-104XC1	8974

23557 7590 12/14/2007
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EXAMINER	
KOSSON, ROSANNE	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
12/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/754,115	HEY ET AL.	
	Examiner	Art Unit	
	Rosanne Kosson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-25 and 34-42* is/are pending in the application.

4a) Of the above claim(s) *38,39 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25,34-37,40 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The amendment filed on October 31, 2007 has been received and entered. Claims 21-25 and 34-42 have been amended. No claims have been canceled or added. The restriction requirement and Applicants' subsequent presentation of claims to non-elected inventions have been discussed at length in the previous Office actions and elsewhere with Applicants. Claims 38, 39 and 42, which depends from 39, still recite non-elected inventions. These claims, therefore, are withdrawn from prosecution as being drawn to non-elected inventions. Accordingly, claims 21-25, 34-37, 40 and 41 are examined on the merits herewith.

Additionally, regarding SEQ ID NOS: 25 and 57 in claims 36, 37 and 41, as well as SEQ ID NOS:22 and 56 in claims 34, 35 and 40, as discussed with Applicants in person and in the previous Office actions, these sequences may be included in the claims when they are recited as whole sequences, because they are known proteins that may be searched by name in text searching. But, because only one protein will be searched per application, one A protein, one B protein and one C protein in the instant application, and because SEQ ID NOS:34, 45 and 47 have been searched, claims reciting fragments of other unsearched sequences and claims reciting proteins having a particular % sequence identity to other unsearched sequences will not be searched. These claims or portions of claims are withdrawn from prosecution as not being drawn to the elected invention. The whole proteins for SEQ ID NOS:25, 57, 22 and 56 were permitted to be recited in the claims in order to provide some claim scope, because the prosecution history did not provide enablement or enablement and written description for sequences having a particular % identity to the elected sequences (SEQ ID NOS:34, 45 and 47), apart from 99% sequence identity as discussed below, or for fragments of the elected

sequences or for hybridization language in the claims. Thus, the portions of claims reciting sequences having 95% or 99% sequence identity to SEQ ID NOS: 25, 57, 22 and 56 (with or without "conservative substitutions") are withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, first paragraph

In view of Applicants' amendments to the claims, the enablement rejection of claims 21-25 is withdrawn. The hybridization language has been deleted and replaced by the transitional phrase "consisting essentially of." Because "consisting essentially of" is not defined in the specification, it is Office policy, particularly with respect to sequences, to interpret this transitional phrase to mean "comprising." Thus, the claims read on a method of inhibiting insects by contacting them with a complex of proteins in which one protein comprises SEQ ID NO:34, a second protein comprises SEQ ID NO:45 (or SEQ ID NO:22 or SEQ ID NO:56) and a third protein comprises SEQ ID NO:47 (or SEQ ID NO:25 or SEQ ID NO:57). See MPEP §2111.03. The claims do not encompass methods in which unspecified, unlimited variations to the aforementioned amino acid sequences have been made. That is, the claims do not include methods in which any number or type of variations to the aforementioned amino acid sequences may be made because Applicants consider these to be non-essential. It cannot be determined from the specification which features Applicants consider to be essential and non-essential for any disclosed protein.

Claims 36, 37 and 41 are again rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of controlling or inhibiting an insect by contacting the insect with a composition comprising SEQ ID NO: 34, plus one of SEQ ID

NOS:22, 45 or 56, plus one of SEQ ID NOS:25, 47 or 57, does not reasonably provide enablement for a method of controlling or inhibiting an insect by contacting the insect with a composition comprising any variant having 95% sequence identity to any or all of the aforementioned proteins, even when the changes to the amino acid sequences are conservative substitutions. Consequently, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

With respect to sequences having a particular % sequence identity to the elected protein sequences, this rejection has been discussed in the previous Office actions. As also discussed in the previous Office actions, Applicants highlighted during their in-person interview on June 7, 2007 that their results are surprising results because there is no correlation between structure and function for the various *Xenorhabdus* and *Photorhabdus* proteins disclosed in the specification. As a result, the function of their complex of SEQ ID NO:34, SEQ ID NO:45 and SEQ ID NO:47, the elected proteins A, B and C (the elected invention) could not have been predicted. According to Applicants, the *Photorhabdus* proteins, SEQ ID NOS:45 and 47 serve as molecular clamp, holding the tetramer of SEQ ID NO:34 (a *Xenorhabdus* protein) together. Because the protein sequences from the different bacteria that are homologous in function differ so widely on the amino acid sequence level, one of skill in the art could not have predicted that the elected B and C clamp proteins from one bacterium would function to maintain the three-dimensional structure of a tetrameric complex of the elected A protein from a second bacterium. Due to this explanation, the obviousness rejection was withdrawn. But, in view of this explanation, the enablement rejection is maintained.

As previously discussed, Applicants have claimed several very large genera of proteins, but have not disclosed any species of these genera. Because Applicants have not disclosed

any species of these claimed genera, and because Applicants have not provided any systematic procedure for identifying these undisclosed species, it cannot be predicted that such species exist. Additionally, it would be undue experimentation to come up with the systematic guidance needed to identify and test these species, and the amount of random make-and-test-for-function experimentation that would be required to practice the full scope of the claims is undue.

Claim 36 recites a method of using a complex comprising SEQ ID NO:34 and SEQ ID NO:47, the elected A and C proteins, or proteins having 95% sequence identity thereto, to inhibit insect growth, a method in which the elected B protein is absent. Although the claim recites that the variant proteins have conservative amino acid substitutions, the mutations are limited by general type only. They are not limited by number. The specification provides no evidence that replacing, e.g., all of the G residues in SEQ ID NO:34 with C and N residues randomly will yield an active protein, particularly in view of the size of this protein. Thus, this new limitation does not serve to overcome the enablement rejection.

As previously noted, all of the claimed proteins are large proteins. SEQ ID NO:34 has 2538 amino acids, SEQ ID NO:45 has 1474 amino acids and SEQ ID NO:47 has 960 amino acids. While methods to produce variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as useful as the native proteins from which the variants are derived requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the activity. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite possibilities. For the rejected claims, because of the size of the proteins, the random making and testing would clearly constitute **undue** experimentation. H. Guo et al. ("Protein Tolerance to Random Amino Acid Change", PNAS 101(25):9205-9210, 2004) teach that the percentage of random single

substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% and that this number appears to be consistent with other studies in other proteins as well. Guo et al. further show in Table 1 and in Equation 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x$ X 100% where x is the number of mutations introduced. Applying this estimate to the instant proteins, for SEQ ID NO:34, 95% identity allows up to 126 mutations, and thus only $(.66)^{126}$ X 100% or 1.8×10^{-23}% of random mutants having 95% sequence identity would be active. Consequently, 5.5×10^{22} clones of mutants would have to be screened to identify one clone that produces an active protein (a protein having the stand-alone insecticidal activity of SEQ ID NO:34). Similarly, for SEQ ID NO:45, 95% identity allows up to 73 mutations, and thus only $(.66)^{73}$ X 100% or 6.7×10^{-14}% of random mutants having 95% sequence identity would be active. Consequently, 1.5×10^{13} clones of mutants would have to be screened to identify one clone that produces an active protein (a protein having the insecticidal enhancing activity of SEQ ID NO:45). Similarly, for SEQ ID NO:47, 95% identity allows up to 48 mutations, and thus only $(.66)^{48}$ X 100% or 2.2×10^{-9}% of random mutants having 95% sequence identity would be active. Consequently, 4.6×10^{8} clones of mutants would have to be screened to identify one clone that produces an active protein (a protein having the insecticidal enhancing activity of SEQ ID NO:47).

Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within about hundred thousand as is the case for the claims limited to 99% identity (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish). But, finding a few mutants within the vast, almost infinite numbers of DNA and protein sequences and clones required for screening as in the claims to 95% sequence identity would not be possible. While enablement

is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

Thus, regarding claims 34, 35 and 40, the enablement rejection with respect to the portions of the claims that recite a method of inhibiting insects by contacting them with a protein complex comprising proteins having 99% sequence identity to SEQ ID NOS:34 and 45 is withdrawn. The portions of the claims that recite using proteins having 99% sequence identity to SEQ ID NOS:22 and 56 are withdrawn.

In view of the foregoing, the rejection of record is maintained.

Double Patenting- Obviousness-Type

Claims 21-25, 34-37, 40 and 41 are again provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 27, 29 and 33 of copending Application No. 11/070,573. This rejection was discussed in the previous Office action. The aforementioned claim numbers are slightly different than in the previous Office action due to Applicants' amendments to the claims, which have caused different claims to be withdrawn. The claims in the copending application have been amended as well.

To reiterate, although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims recite a method of controlling or inhibiting an insect, comprising contacting the insect with a composition comprising Proteins A, B and C (SEQ ID NOS:34, 45 (or 22 or 56) and 47 (or 25 or 57), respectively), while the copending claims recite a method of preventing an insect from feeding on a plant, a more specific form of inhibition, comprising contacting the insect with a composition comprising Proteins A, B and C

(SEQ ID NOS:23, 6 (or 5 or 7) and 14 (or 12 or 16), respectively, which are the same sequences as instant SEQ ID NOS:34, 45 (or 22 or 56) and 47 (or 25 or 57)). In the copending application, Proteins B and C are part of a fusion protein, while, in the instant application, Proteins B and C may or may not be linked in a fusion protein (although the three proteins are all encoded by one vector- see, e.g., pp. 63-66 and 90 of the instant specification), but the copending claims are a narrower version of the instant claims. These two claim sets would not have been restricted apart had they been presented together in one application.

Applicants assert that the copending application was filed after the instant application. Applicants assert that the copending claims are not an obvious variation of the instant claims, because one of skill in the art would have had no expectation that these fusion proteins would be active and that it was a complete surprise that they were found to be active.

In reply, for an ODP (obviousness-type double patenting) rejection between two copending applications, it does not matter which application was filed first. If both applications have been filed, and if neither case contains the required ODP rejection, the rejection will be made in the case presenting the first opportunity to make the rejection. If the earlier filed of the two applications is otherwise in condition for allowance, the ODP rejection will be dropped and maintained in the other application until a terminal disclaimer is filed. For treatment of the situation where the later filed application becomes allowable see MPEP 804 I (B) (1).

The instant claims are anticipated by the copending claims. Applicants' argument that the copending claims are not an obvious variant of the instant claims does not serve to overcome the ODP rejection, because the rejection is that the instant claims are anticipated by the copending claims. ODP does not require two-way obviousness. Applicants have not explained why the current instant claims are not anticipated or obvious over the copending claims, not the reverse as Applicants have argued. Whether or not the fusion proteins in the

copending case are active is not relevant here, as the instant claims do not recite fusion proteins.

Nevertheless, as for expecting the fusion proteins to be inactive, the copending application carries with it a presumption and an expectation that the invention described therein does work, certainly for the majority of the disclosed embodiments. Thus, one of skill in the art would have expected the fusion proteins disclosed therein to be functional for their stated purposes.

In view of the foregoing, the rejection of record is still outstanding and is maintained.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rosanne Kosson whose telephone number is 571-272-2923. The examiner can normally be reached on Monday-Friday, 8:30-6:00, alternate Mondays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rosanne Kosson
Examiner, Art Unit 1652
rk/2007-12-06

Rosanne Kosson

/Rebecca Prouty/
Primary Examiner
Art Unit 1652